

- 1. A method for screening for susceptibility to infection comprising:
  - a) obtaining sample nucleic acid from an animal; and

b) analyzing the sample nucleic acid to detect a mutation in a gene encoding a TLR-4 polypeptide relative to a sequence of a gene encoding a native TLR-4 polypeptide;

wherein a mutation in the gene encoding the TLR-4 polypeptide is indicative of susceptibility to infection.

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- 2. The method of claim 1, wherein the sample nucleic acid is DNA.
- 3. The method of claim 1, wherein the step of analyzing the sample nucleic acid comprises sequencing the nucleic acid to obtain a sequence.

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- 4. The method of claim 3 wherein the obtained sequence is compared to a nucleic acid sequence from a gene encoding a native TLR-4 polypeptide.
- 5. The method of claim 1, wherein the sequence of the gene encoding a native TLR4 polypeptide has a nucleic acid sequence set forth in SEQ ID NO:1, SEQ ID NO:3; SEQ ID NO:5, SEQ ID NO:46, SEQ ID NO:47 or SEQ ID NO:48.
  - 6. The method of claim 1, wherein the native TLR-4 polypeptide has an amino acid sequence set forth in of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.
  - 7. The method of claim 1, wherein the sample nucleic acid comprises a mutation that results in a change in amino acid sequence of the encoded TLR-4 polypeptide relative to the amino acid sequence of a native TLR-4 polypeptide.

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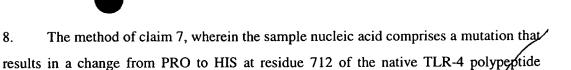
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amino acid sequence of SEQ ID NO:99.



- 9. The method of claim 7, wherein the sample nucleic acid comprises a mutation that results in a change from GLU to LYS at residue 178, a change from ARG to HIS at residue 763, a change from GLN to ARG at residue 188, a change from ASP to GLY at residue 299, a change from ASN to SER at residue 329, a change from GLU to LYS at residue 474, a change from ARG to HIS at residue 763, a change from TYR to CYS at residue 46, a change from PRO to HIS at residue 145, a change from CYS to TYR at residue 281, a change from ASN to HIS at residue 624, or a change from THR to ILE at residue 399 of the native TLR-4 polypeptide amino acid sequence of SEQ ID NO:98.
  - The method of claim 9, wherein the sample nucleic acid comprises at least a 10. second mutation.
  - The method of claim 10, wherein said second mutation results in a deletion of 11. VAL-GLY-THR at residues 827-829/of the native TLR-4 polypeptide amino acid sequence of SEQ ID NO:98.
  - The method of claim 3, wherein the sample nucleic acid comprises at least one 12. point mutation relative to a nucleic acid sequence from a gene encoding a native TLR-4 polypeptide.
- The method of claim 12, wherein the sample nucleic acid comprises at least two 25 13. point mutations relative to a nucleic acid sequence from a gene encoding a native TLR-4 polypeptide.
- The method of claim 12, wherein said mutation is in nucleotide 2342 of the nucleic acid sequence of SEQ ID NO:46. 30

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- 15. The method of claim 14, wherein said at least one mutation is a change from nucleotide C to nucleotide A at position 2342 of the nucleic acid sequence.
- 5 16. The method of claim 12, wherein said at least one mutation is in Exon 2, Exon 3 or Intron 2 of the sequence of SEQ ID NO:47.
  - 17. The method of claim 16, wherein said at least one mutation is a change from nucleotide A to nucleotide G at position 8457, a change from nucleotide G to nucleotide A at position 8612, a change from nucleotide A to nucleotide G at position 12245, a change from nucleotide T to nucleotide C at position 12293, a change from nucleotide C to nucleotide A at position 12412, a change from nucleotide C to nucleotide A at position 12413, a change from nucleotide G at position 12541, a change from nucleotide G at position 12541, a change from nucleotide G to nucleotide A at position 12820, a change from nucleotide A to nucleotide G at position 12964, a change from nucleotide C to nucleotide T at position 13174, a change from nucleotide G to nucleotide A at position 13398, a change from nucleotide G to nucleotide A at position 13769, a change from nucleotide A to nucleotide C at position 13848, a change from nucleotide G to nucleotide A at position 13937, or a change from nucleotide G to nucleotide A at position 134266 of the sequence of SEQ ID NO:47.
  - 18. The method of claim 16, wherein said at least one mutation is a deletion of nucleotide T at position 12228 of the sequence of SEQ ID NO:47.
  - 19. The method of claim 16, wherein said at least one mutation is a change from nucleotide A to nucleotide G at position 12245 of the gene sequence and a deletion of nucleotides 14453 to 14461 of the sequence of SEQ ID NO:47.





- 20. The method of claim 16, wherein the sample nucleic acid sequence comprises at least two mutations relative to the sequence of SEQ ID NO:47.
- 21. The method of claim 20, wherein said at least two mutations comprise a change from nucleotide C to nucleotide T at position 12399 and a change from nucleotide G to nucleotide A at position 12510, a change from nucleotide C to nucleotide A at position 12413 and a change from nucleotide G to nucleotide A at position 14266, or a change from nucleotide A to nucleotide G at position 12874 and a change from nucleotide C to nucleotide T at position 13174 of the sequence of SEQ ID NØ:47.

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- 22. The method of claim 1, wherein the step of analyzing the sample nucleic acid comprises PCR, an RNase protection assay, or an RFLP procedure.
- 23. A method of reducing susceptibility of an animal to infection comprising the step of modulating an LPS mediated response in the animal.
  - 24. The method of claim 22, further comprising the step of diagnosing an animal with an infection via analysis of a TLR-4-encoding nucleic acid sequence for a mutation relative to a sequence of a gene encoding a native TLR-4 polypeptide.

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25. The method of claim 24, wherein the native TLR-4 polypeptide is a TLR-4 polypeptide that has the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.

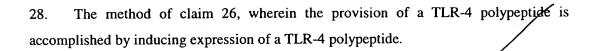
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- 26. The method of claim 22, wherein the step of modulating LPS receptor function comprises providing a TLR-4 polypeptide to the animal.
- 27. The method of claim 26, wherein the TLR-4 polypeptide is a native TLR-4 polypeptide.

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- 5 29. The method of claim 28, wherein the expression of a TLR-4 polypeptide encoded in the animal's genome is induced.
  - 30. The method of claim 28, wherein the expression of a TLR-4 polypeptide encoded by a nucleic acid provided to the animal is induced.

31. The method of claim 26, wherein the provision of a TLR-4 polypeptide is accomplished by a method comprising introduction of a TLR-4-encoding nucleic acid to the animal.

- 15 32. The method of claim 26, wherein the provision of a TLR-4 polypeptide is accomplished by injecting a TLR-4 polypeptide into the animal.
  - 33. The method of claim 23, wherein the step of modulating LPS receptor function in the animal comprises providing a modulator of TLR-4 to the animal.
  - 34. The method of claim 33, wherein the modulator of TLR-4 is an agonist of TLR-4.
  - 35. The method of claim 33, wherein the modulator of TLR-4 is an antagonist of TLR-4.
  - 36. The method of claim 33, wherein the modulator of TLR-4 modulates transcription of a TLR-4-encoding nucleic acid.
  - / 37. The method of claim 33, wherein the modulator of TLR-4 modulates translation of a TLR-4-encoding nucleic acid.

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- 38. A method of screening for modulators of an LPS mediated response comprising the steps of:
  - a) obtaining a TLR-4 polypeptide;
  - b) determining a standard activity profile of the TLR-4 polypeptide;
  - c) contacting the TLR-4 polypeptide with a putative modulator; and
  - d) assaying for a change in the standard activity profile.
- 39. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.

- 40. The method of claim 39, wherein the standard activity profile of the TLR-4 polypeptide is determined by determining the ability of the TLR-4 polypeptide to stimulate transcription of a reporter gene, the reporter gene operatively positioned under control of a nucleic acid segment comprising a promoter from a TLR-4 gene.
- 41. A method of modulating an LPS mediated response comprising modulating TLR-4 function in an animal.

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- 42. The method of claim 41, further comprising the step of diagnosing the animal for susceptibility to infection via analysis of a TLR-4 encoding nucleic acid sequence for a mutation relative to a sequence of a gene encoding a native TLR-4 polypeptide.
- 25 43. The method of claim 41, comprising providing a TLR-4 polypeptide to the animal.
  - 44. The method of claim 43, wherein the TLR-4 polypeptide is a TLR-4 polypeptide that has the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.



- 45. The method of claim 43, wherein the provision of a TLR-4 polypeptide is accomplished by inducing expression of a TLR-4 polypeptide.
- 5 46. The method of claim 43, wherein the provision of a TLR-4 polypeptide is accomplished by a method comprising introduction of a TLR-4-encoding nucleic acid to the animal.
- 47. The method of claim 43, wherein the provision of a TLR-4 polypeptide is accomplished by injecting a TLR-4 polypeptide into the animal.
  - 48. The method of claim 41, wherein the step of modulating TLR-4 function in the animal comprises providing a modulator of TLR-4 to the animal.
- 15 49. The method of claim 48, wherein the modulator of TLR-4 is an agonist of TLR-4.
  - 50. The method of claim 48, wherein the modulator of TLR-4 modulates transcription of a TLR-4-encoding nucleic acid.
- 20 51. The method of claim 48, wherein the modulator of TLR-4 modulates translation of a TLR-4-encoding nucleic acid.

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